MicroRNA-mediated conversion of human fibroblasts to neurons.

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Public Summary:
Neurogenic transcription factors and evolutionarily conserved signalling pathways have been found to be instrumental in the formation of neurons. However, the instructive role of microRNAs (miRNAs) in neurogenesis remains unexplored. We recently discovered that miR-9* and miR-124 instruct compositional changes of SWI/SNF-like BAF chromatin-remodeling complexes, a process important for neuronal differentiation and function. Nearing mitotic exit of neural progenitors, miR-9* and miR-124 repress the BAF53a subunit of the neural-progenitor (np)BAF chromatin-remodeling complex. After mitotic exit, BAF53a is replaced by BAF53b, and BAF45a by BAF45b and BAF45c, which are then incorporated into neuron-specific (n)BAF complexes essential for post-mitotic functions. Because miR-9/9* and miR-124 also control multiple genes regulating neuronal differentiation and function, we proposed that these miRNAs might contribute to neuronal fates. Here we show that expression of miR-9/9* and miR-124 (miR-9/9*-124) in human fibroblasts induces their conversion into neurons, a process facilitated by NEUROD2. Further addition of neurogenic transcription factors ASCL1 and MYT1L enhances the rate of conversion and the maturation of the converted neurons, whereas expression of these transcription factors alone without miR-9/9*-124 was ineffective. These studies indicate that the genetic circuitry involving miR-9/9*-124 can have an instructive role in neural fate determination.

Scientific Abstract:
Neurogenic transcription factors and evolutionarily conserved signalling pathways have been found to be instrumental in the formation of neurons. However, the instructive role of microRNAs (miRNAs) in neurogenesis remains unexplored. We recently discovered that miR-9* and miR-124 instruct compositional changes of SWI/SNF-like BAF chromatin-remodelling complexes, a process important for neuronal differentiation and function. Nearing mitotic exit of neural progenitors, miR-9* and miR-124 repress the BAF53a subunit of the neural-progenitor (np)BAF chromatin-remodelling complex. After mitotic exit, BAF53a is replaced by BAF53b, and BAF45a by BAF45b and BAF45c, which are then incorporated into neuron-specific (n)BAF complexes essential for post-mitotic functions. Because miR-9/9* and miR-124 also control multiple genes regulating neuronal differentiation and function, we proposed that these miRNAs might contribute to neuronal fates. Here we show that expression of miR-9/9* and miR-124 (miR-9/9*-124) in human fibroblasts induces their conversion into neurons, a process facilitated by NEUROD2. Further addition of neurogenic transcription factors ASCL1 and MYT1L enhances the rate of conversion and the maturation of the converted neurons, whereas expression of these transcription factors alone without miR-9/9*-124 was ineffective. These studies indicate that the genetic circuitry involving miR-9/9*-124 can have an instructive role in neural fate determination.